PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-2661	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11457	International filing date *(day/month/year)* 13.10.2003	Priority date *(day/month/year)* 11.10.2002
International Patent Classification (IPC) or both national classification and IPC C07H15/04		
Applicant YAMANOUCHI EUROPE B.V. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.05.2004	17.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Fitz, W Telephone No. +31 70 340-4359

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11457

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-17 as originally filed

Claims, Numbers

1-15 received on 23.12.2004 with letter of 23.12.2004

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: US-A-5 830 871

1.) The document D1 is regarded as being the closest prior art, and shows (cf. Figure 5) a glucose-based compound with affinity to P-selectin.
The presently claimed compounds mainly differ from this known compound in that they have a 2-substituent comprising at least one carbon atom (whereas the compound of D1 has an OH-group at the 2-position).
Accordingly, the subject-matter of claims 1-15 is new (Article 33(2) PCT).

2.) The problem to be solved by the present invention may be regarded as the provision of further glucose-based compounds with affinity to P-selectin.
D1 alone, or in combination with another document of the prior art, would not direct the skilled person towards compounds having a 2-substituent comprising at least one carbon atom in place of the usual 2-OH group.
Accordingly, the subject-matter of claims 1-15 is considered as involving an inventive step (Article 33(3) PCT).

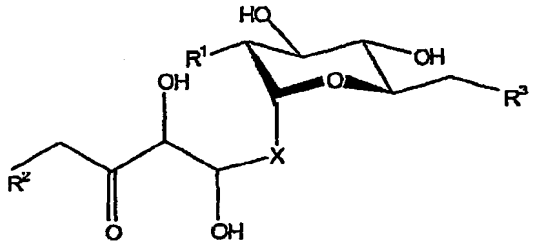
3.) In claims 1,8 and 10-15, the definition of the R1 group as "QR4...wherein R4 represents any substituent comprising at least one carbon atom" is broad. From the description on page 8, last paragraph it is clear that the substituent R1 is "critical" and "plays an active role in the recognition of or selectivity to P-selectin".
In conclusion, because of the broadness of the term "any substituent comprising at least one carbon atom" and because of the critical importance of the nature of the R1 group, the present claims are not supported by the description over their whole scope, as is required by Article 6 PCT.

4.) The terms "R2 is a moiety bearing at least one negative charge" used in claims 1,8,10-15, "R3 can be any group" used in claims 1,10-15, and "R3 can be any group wherein R3 comprises an anchor moiety capable of anchoring the compound to a colloidal or microparticulate drug carrier" are broad and/or vague. It should be ensured that the scope of the claims is commensurate with the support and the disclosure.

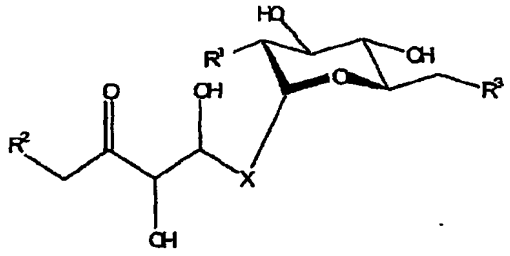
5.) Present compounds are of interest for pharmaceutical purposes. Accordingly, the subject-matter of claims 1-15 is considered as industrially applicable.

CLAIMS

1. Compounds having affinity to and/or selectivity for P-selectin, represented by the following formula Ia:



and their stereo-isomers, represented by the following formula Ib:



wherein:
X is an optional group, which represents -O-, -OCH_2-, -S-, -SCH_2-, -NH- or -$NHCH_2$-;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group.

2. The compounds according to claim 1, wherein X is not present or represents -O-.

3. The compounds according to any one of the preceding claims, wherein Q represents -NH-(C=O)-.

4. The compounds according to any one of the preceding claims, wherein R^2 is or comprises a phosphate group.

5. The compounds according to any one of the preceding claims, wherein R^3 represents OH or YR^5, wherein Y is -O-, $-CH_2-$ or -NH- and R^5 comprises at least one carbon atom.

6. The compounds according to any one of the preceding claims, wherein R^4 comprises an alkyl moiety, an aromatic moiety or a group comprising an electron withdrawing moiety.

7. The compounds according to claim 6, wherein R^4 is a phenyl or a naphthalene group.

8. Compounds having affinity to and/or selectivity for P-selectin, represented by the formula Ia, and their stereo-isomers, represented by the formula Ib, wherein:
X is an optional group, which represents -O-, $-OCH_2-$, -S-, $-SCH_2-$, -NH- or $-NHCH_2-$;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group,
wherein R^3 comprises an anchor moiety capable of anchoring the compound to a colloidal or microparticulate drug carrier.

9. The compounds according to claim 8, wherein the anchor moiety is a peptide or peptidomimetic moiety having affinity to P-selectin.

10. Compounds having affinity to and/or selectivity for P-selectin, represented by the formula Ia, and their stereo-isomers, represented by the formula Ib, wherein:
X is an optional group, which represents -O-, $-OCH_2-$, -S-, $-SCH_2-$, -NH- or $-NHCH_2-$;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group,
as a diagnostic agent or a medicament.

11. Compounds having affinity to and/or selectivity for P-selectin, represented by the formula Ia, and their stereo-isomers, represented by the formula Ib, wherein:
X is an optional group, which represents -O-, -OCH_2-, -S-, -SCH_2-, -NH- or -$NHCH_2$-;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group,
as an antagoniser for P-selectin.

12. Compounds having affinity to and/or selectivity for P-selectin, represented by the formula Ia, and their stereo-isomers, represented by the formula Ib, wherein:
X is an optional group, which represents -O-, -OCH_2-, -S-, -SCH_2-, -NH- or -$NHCH_2$-;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group,
as a targeting agent to deliver a pharmaceutically active compound to a cell or to tissue expressing P-selectin.

13. Use of compounds having affinity to and/or selectivity for P-selectin, represented by the formula Ia, and their stereo-isomers, represented by the formula Ib, wherein:
X is an optional group, which represents -O-, -OCH_2-, -S-, -SCH_2-, -NH- or -$NHCH_2$-;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group,
in the manufacture of a medicament for the diagnosis, prevention or inhibition of a disease or condition involving the activation or overexpression of P-selectin.

14. Pharmaceutical composition, comprising in a pharmaceutically acceptable carrier a compound having affinity to and/or selectivity for P-selectin, represented by the formula Ia, and its stereo-isomer, represented by the formula Ib, wherein:
X is an optional group, which represents -O-, $-OCH_2-$, -S-, $-SCH_2-$, -NH- or $-NHCH_2-$;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group,
or a derivative, salt, conjugate, solvate, or multimer thereof.

15. A method for determining whether a compound is capable of binding to P-selectin or a functional equivalent of P-selectin, comprising contacting and incubating the compound to be tested and a predetermined amount of a compound having affinity to and/or selectivity for P-selectin, represented by the formula Ia, and its stereo-isomer, represented by the formula Ib, wherein:
X is an optional group, which represents -O-, $-OCH_2-$, -S-, $-SCH_2-$, -NH- or $-NHCH_2-$;
R^1 represents QR^4, wherein Q represents -O-, -NH-, -NH-(C=O)-, -O-(C=O), -NH-(C=O)-O- or -NH-(C=O)-NH-; and wherein R^4 represents any substituent comprising at least one carbon atom;
R^2 is a moiety bearing at least one negative charge and
R^3 can be any group,
with a predetermined amount of P-selectin or said functional equivalent of P-selectin and subsequently determining the amount of the same compound.